

CLAIMS

What is claimed is:

1. A cell adhesion modulating agent that
 - (a) modulates cadherin-mediated cell adhesion; and
 - (b) comprises
 - (i) an amino acid sequence Asp/Glu-Trp-Val-Ile/Val/Met-Pro/Ala-Pro (SEQ ID NO:1), but contains no more than 50 consecutive amino acid residues present within a cadherin molecule; wherein Asp/Glu is an amino acid that is either Asp or Glu, Ile/Val/Met is an amino acid selected from the group consisting of Ile, Val and Met, and Pro/Ala is either Pro or Ala;
 - (ii) a conservative analogue of SEQ ID NO:1;
 - (iii) an antibody or antigen-binding fragment thereof that specifically binds to SEQ ID NO:1; or
 - (iv) a peptidomimetic of SEQ ID NO:1.
2. The cell adhesion modulating agent of claim 1 wherein the agent comprises SEQ ID NO:1 that is present within a linear peptide.
3. The cell adhesion modulating agent of claim 1 wherein the agent comprises SEQ ID NO:1 that is present within the ring of a cyclic peptide.
4. The cell adhesion modulating agent of claim 3 wherein the size of the ring is from 6 to 15 amino acids.
5. The cell adhesion modulating agent of claim 1 wherein the agent is a peptide ranging in size from 6 to 50 amino acid residues.

6. The cell adhesion modulating agent of claim 5 wherein the agent is a peptide ranging in size from 6 to 15 amino acid residues.

7. The cell adhesion modulating agent of claim 1 wherein the cell adhesion modulating agent is a peptide comprising SEQ ID NO:1 or a conservative analogue thereof.

8. The cell adhesion modulating agent of claim 7 wherein the peptide comprises an N-terminal or C-terminal modification.

9. The cell adhesion modulating agent of claim 8 wherein the N-terminal modification is N-acetylation.

10. The cell adhesion modulating agent of claim 1 linked to a heterologous compound.

11. The cell adhesion modulating agent of claim 10 wherein the heterologous compound is a pharmaceutically active compound.

12. The cell adhesion modulating agent of claim 1 linked to a solid support.

13. The cell adhesion modulating agent of claim 1 further comprising a cell adhesion recognition sequence other than SEQ ID NO:1 wherein the cell adhesion recognition sequence is separated from SEQ ID NO:1 by a linker.

14. The cell adhesion modulating agent of claim 1 further comprising an antibody or antigen-binding fragments thereof that specifically binds to a cell adhesion recognition sequence other than SEQ ID NO:1.

15. The cell adhesion modulating agent of claim 1 further comprising
 - (a) a cell adhesion recognition sequence other than SEQ ID NO:1 wherein the cell adhesion recognition sequence is separated from SEQ ID NO:1 by a linker, and
 - (b) an antibody or antigen-binding fragments thereof that specifically binds to a cell adhesion recognition sequence other than SEQ ID NO:1.

16. A composition comprising a cell adhesion modulating agent of claim 1 in combination with a physiologically acceptable carrier.

17. A method for modulating cell adhesion, comprising contacting a cell that expresses a cadherin with a cell adhesion modulating agent of claim 1 and thereby modulating cell adhesion.

18. The method according to claim 17, wherein the cell is selected from the group consisting of epithelial cells, endothelial cells, neural cells, tumor cells and lymphocytes.

19. The method according to claim 17, wherein the cadherin is E-cadherin.

20. The method according to claim 17, wherein the cadherin is N-cadherin.

21. The method according to claim 17, wherein the cadherin is P-cadherin.

22. The method according to claim 17, wherein the cadherin is R-cadherin.

23. The method according to claim 17, wherein the cell adhesion modulating agent inhibits cadherin-mediated cell adhesion.

24. The method according to claim 17, wherein the cell adhesion modulating agent enhances cadherin-mediated cell adhesion.

25. A method for reducing the progression of a cancer in a mammal, comprising administering to a mammal having a cancer a modulating agent according to claim 1 and thereby reducing the progression of the cancer in the mammal, wherein the modulating agent inhibits cadherin mediated cell adhesion.

26. A method for reducing unwanted cellular adhesion in a mammal, comprising administering to a mammal with unwanted cellular adhesion a modulating agent of claim 1 and thereby reducing unwanted cellular adhesion, wherein the modulating agent inhibits cadherin mediated cell adhesion.

27. A method for enhancing the delivery of a pharmaceutical active substance through the skin of a mammal, comprising contacting epithelial cells of a mammal with a pharmaceutical active substance and a modulating agent according to claim 1 and thereby enhancing the delivery of the substance through the skin, wherein the step of contacting is performed under conditions and for a time sufficient to allow passage of the substance across the epithelial cells, and wherein the modulating agent inhibits cadherin mediated cell adhesion.

28. A method for enhancing the delivery of a pharmaceutically active substance to a tumor in a mammal, comprising contacting the tumor with a pharmaceutically active substance and a modulating agent according to claim 1 and thereby enhancing the delivery of the substance to the tumor, wherein the step of contacting is performed under conditions and for a time sufficient to allow passage of the substance into the cells of the tumor, and wherein the modulating agent inhibits cadherin mediated cell adhesion.

29. A method for inhibiting cancer metastasis comprising administrating to a mammal having a cancer with a modulating agent according to claim 1 and thereby inhibiting metastasis of the cancer.

30. A method for inducing apoptosis in a cadherin-expressing cell, comprising contacting a cadherin-expressing cell with a modulating agent according to claim 1 and thereby inducing apoptosis in the cell, wherein the modulating agent inhibits cadherin mediated cell adhesion.

31. A method for inhibiting angiogenesis in a mammal, comprising administering to a mammal a modulating agent according to claim 1 and thereby inhibiting angiogenesis in the mammal, wherein the modulating agent inhibits cadherin mediated cell adhesion.

32. A method for enhancing the delivery of a pharmaceutically active substance to the central nervous system of a mammal, comprising administering to a mammal a modulating agent according to claim 1 and thereby enhancing the delivery of a pharmaceutically active substance, wherein the modulating agent inhibits cadherin mediated cell adhesion.

33. A method for ameliorating a demyelinating neurological disease in a mammal, comprising administering to a mammal with a demyelinating neurological disease a modulating agent according to claim 1 and thereby ameliorating the demyelinating neurological disease, wherein the modulating agent inhibits cadherin mediated cell adhesion.

34. A method for modulating the immune system of a mammal, comprising administering to a mammal a modulating agent according to claim 1 and thereby modulating the immune system of the mammal, wherein the modulating agent inhibits cadherin mediated cell adhesion.

35. A method for preventing pregnancy in a mammal, comprising administering to a mammal a modulating agent according to claim 1 and thereby preventing pregnancy in the mammal, wherein the modulating agent inhibits cadherin mediated cell adhesion.

36. A method for increasing vasopermeability in a mammal, comprising administering to a mammal a modulating agent according to claim 1 and thereby increasing vasopermeability in the mammal, wherein the modulating agent inhibits cadherin mediated cell adhesion.

37. A method for inhibiting synaptic stability in a mammal, comprising administering to a mammal a modulating agent according to claim 1 and thereby inhibiting synaptic stability in the mammal, wherein the modulating agent inhibits cadherin mediated cell adhesion.

38. A method for facilitating blood sampling in a mammal, comprising contacting epithelial cells of a mammal with a cell adhesion modulating agent according to claim 1 and thereby facilitating blood sampling in the mammal, wherein the step of contacting is performed under conditions and for a time sufficient to allow passage of one or more blood components across the epithelial cells, wherein the modulating agent inhibits cadherin mediated cell adhesion.

39. A method for facilitating migration of an N-cadherin expressing cell on astrocytes, comprising contacting an N-caderin expressing cell with:

- (a) a cell adhesion modulating agent according to claim 1; and
- (b) one or more astrocytes;

and thereby facilitating migration of the N-cadherin expressing cell on astrocytes, wherein the modulating agent inhibits cadherin mediated cell adhesion.

40. A method for stimulating blood vessel regression, comprising administering to a mammal a cell adhesion modulating agent according to claim 1 and thereby stimulating blood vessel regression, wherein the modulating agent inhibits cadherin mediated cell adhesion.

41. A method for reducing aggregation of cultured cells, comprising contacting cultured stem cells with a cell adhesion modulating agent of claim 1 and thereby reducing aggregation of stem cells, wherein the modulating agent inhibits cadherin mediated cell adhesion.

42. The method according to claim 41 wherein the cultured cells are stem cells.

43. A method for increasing blood flow to a tumor in a mammal, comprising administering to a mammal the cell adhesion modulating agent of claim 1 and thereby increasing blood flow to a tumor in the mammal, wherein the agent inhibits endothelial cell adhesion.

44. A method of disrupting neovasculature in a mammal, comprising administering to a mammal a cell adhesion modulating agent of claim 1 and thereby disrupting neovasculature, wherein the modulating agent inhibits cadherin mediated cell adhesion.

45. A method for inhibiting endometriosis in a mammal, comprising administering to a mammal a cell adhesion modulating agent of claim 1 and thereby inhibiting endometriosis, wherein the modulating agent inhibits cadherin mediated cell adhesion.

46. A method for enhancing inhaled compound delivery in a mammal, comprising contacting lung epithelial cells of a mammal with a cell adhesion modulating agent of

claim 1 and thereby enhancing inhaled compound delivery, wherein the modulating agent inhibits cadherin mediated cell adhesion.

47. A method for facilitating wound healing in a mammal, comprising contacting a wound in a mammal with a cell adhesion modulating agent according to claim 1 and thereby facilitating wound healing, wherein the modulating agent enhances cadherin-mediated cell adhesion.

48. A method for enhancing adhesion of a foreign tissue implanted within a mammal, comprising contacting a site of implantation of a foreign tissue in a mammal with a cell adhesion modulating agent according to claim 1 and thereby enhancing adhesion of the foreign tissue, wherein the modulating agent enhances cadherin-mediated cell adhesion.

49. A method for enhancing and/or directing neurite outgrowth, comprising contacting a neuron with a cell adhesion modulating agent according to claim 1 and thereby enhancing and directing neurite outgrowth, wherein the modulating agent enhances cadherin-mediated cell adhesion.

50. A method of ameliorating a spinal cord injury in a mammal, comprising administering to a mammal having a spinal cord injury a cell adhesion modulating agent according to claim 1, wherein the modulating agent enhances cadherin-mediated cell adhesion, and thereby ameliorating the spinal cord injury.

51. A kit for enhancing transdermal delivery of a pharmaceutically active substance, comprising:

- (a) a skin patch; and
- (b) a cell adhesion modulating agent according to claim 1.

52. A method for screening a candidate compound for the ability to modulate classical cadherin-mediated cell adhesion, comprising comparing a three-dimensional structure of a candidate compound to a three-dimensional structure of a peptide having an amino acid sequence as set forth in SEQ ID NO:1 and a cell adhesion modulating activity, wherein similarity between the structure of the candidate compound and the structure of the peptide is indicative of the ability of the candidate compound to modulate classical cadherin-mediated cell adhesion, and therefrom evaluating the ability of the candidate compound to modulate classical cadherin-mediated cell adhesion.

53. A method for identifying a compound that modulates classical cadherin-mediated cell adhesion, comprising:

- (a) determining a level of similarity between a three-dimensional structure of a candidate compound and a three-dimensional structure of a peptide having an amino acid sequence as set forth in SEQ ID NO:1 and a cell adhesion modulating activity; and
- (b) identifying an alteration in the structure of the candidate compound that results in a three-dimensional structure with an increased similarity to the three-dimensional structure of the peptide; and therefrom identifying a compound that has the ability to modulate classical cadherin-mediated cell adhesion.

54. A method for evaluating a peptidomimetic for the ability to modulate classical cadherin-mediated cell adhesion, comprising:

- (a) culturing neurons on a monolayer of cells that express N-cadherin in the presence and absence of a peptidomimetic, under conditions and for a time sufficient to allow neurite outgrowth, wherein the peptidomimetic has a three-dimensional structure that is substantially similar to a three-dimensional structure of a peptide having an amino acid sequence as set forth in SEQ ID NO:1 and a cell adhesion modulating activity;
- (b) determining a mean neurite length for said neurons; and

(c) comparing the mean neurite length for neurons cultured in the presence of peptidomimetic to the neurite length for neurons cultured in the absence of the peptidomimetic, and therefrom determining whether the peptidomimetic modulates classical cadherin-mediated cell adhesion.

55. A method for evaluating a peptidomimetic for the ability to modulate classical cadherin-mediated cell adhesion, comprising:

(a) culturing cells that express a classical cadherin in the presence and absence of a peptidomimetic, under conditions and for a time sufficient to allow cell adhesion, wherein the peptidomimetic has a three-dimensional structure that is substantially similar to a three-dimensional structure of a peptide having an amino acid sequence as set forth in SEQ ID NO:1 and a cell adhesion modulating activity; and

(b) visually evaluating the extent of cell adhesion among said cells, and therefrom identifying a peptidomimetic capable of modulating cell adhesion.

56. A method for evaluating a peptidomimetic for the ability to modulate classical cadherin-mediated cell adhesion, comprising:

(a) culturing NRK cells in the presence and absence of a peptidomimetic, under conditions and for a time sufficient to allow cell adhesion, wherein the peptidomimetic has a three-dimensional structure that is substantially similar to a three-dimensional structure of a peptide having an amino acid sequence as set forth in SEQ ID NO:1 and a cell adhesion modulating activity; and

(b) comparing the level of cell surface E-cadherin for cells cultured in the presence of the peptidomimetic to the level for cells cultured in the absence of the peptidomimetic, and therefrom determining whether the peptidomimetic modulates cell adhesion.

57. A method for evaluating a peptidomimetic for the ability to modulate classical cadherin-mediated cell adhesion, comprising:

(a) contacting an epithelial surface of skin with a test marker in the presence and absence of a peptidomimetic, wherein the peptidomimetic has a three-dimensional structure that is substantially similar to a three-dimensional structure of a peptide having an amino acid sequence as set forth in SEQ ID NO:1 and a cell adhesion modulating activity; and

(b) comparing the amount of test marker that passes through said skin in the presence of the peptidomimetic to the amount that passes through skin in the absence of the peptidomimetic, and therefrom determining whether the peptidomimetic modulates cell adhesion.

58. A method for evaluating the ability of a peptidomimetic to modulate classical cadherin-mediated cell adhesion, comprising:

(a) contacting a blood vessel with a peptidomimetic, wherein the peptidomimetic has a three-dimensional structure that is substantially similar to a three-dimensional structure of a peptide having an amino acid sequence as set forth in SEQ ID NO:1; and

(b) comparing the extent of angiogenesis of the blood vessel to a predetermined extent of angiogenesis observed for a blood vessel in the absence of the peptidomimetic, and therefrom determining whether the peptidomimetic modulates cell adhesion.

59. A cell adhesion modulating agent comprising the structure provided in Compound I.

60. A process for manufacturing a compound that modulates cell adhesion comprising

(a) performing any one of the methods according to claims 52-53; and

(b) producing the compound identified in step (a).

61. A process for manufacturing a peptidomimetic that modulates cell adhesion comprising

- (a) performing any one of the methods according to claims 54-58; and
- (b) producing the peptidomimetic if the peptidomemetic has the ability to modulate classical cadherin-mediated cell adhesion.